Prevention and Schizophrenia—The Role of Dietary Factors

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Adequate prenatal nutrition is essential for optimal brain development. There is a growing body of evidence from epidemiology linking exposure to nutritional deprivation and increased risk of schizophrenia. Based on studies from the Netherlands and China, those exposed to macronutrient deficiencies during famine have an increased risk of schizophrenia. With respect to micronutrients, we focus on 3 candidates where there is biological plausibility for a role in this disorder and at least 1 study of an association with schizophrenia. These nutrients include vitamin D, folic acid, and iron. While the current evidence is incomplete, we discuss the potential implications of these findings for the prevention of schizophrenia. We argue that schizophrenia can draw inspiration from public health interventions related to prenatal nutrition and other outcomes and speculate on relevant factors that bear on the nature, risks, impact, and logistics of various nutritional strategies that may be employed to prevent this disorder.

Key words: nutrition/epidemiology/prevention/ schizophrenia

Introduction

Nutritional deprivation (ND) represents one of the greatest public health challenges throughout the world. The prevalence of maternal undernutrition varies from 10% to 19% in most countries, although the most deprived countries, such as those in South Asia and Africa, experience a prevalence of approximately 40%.[1] Subjects who are nutritionally deprived may suffer from both macro- and micronutrient deficiencies. Although macronutrient deficiency is not common in high-income countries, where food is more plentiful and obesity is more of a problem, deficiencies of micronutrients have a surprisingly high prevalence.

Pregnancy is a time of increased nutrient demand in order to satisfy normal fetal growth and development, resulting in an even higher prevalence of ND in this population, and, as reviewed below, ND during pregnancy is a major cause of disease and disability in the offspring. Hence, there is a pressing need for preventive nutritional interventions during pregnancy.

ND during gestation and infancy represents one of the most common causes of neurodevelopmental disorders, and, as reviewed elsewhere, schizophrenia is likely rooted in deviations in neurodevelopment.[2,3] Hence, the role of prenatal ND has been investigated as a potential etiologic factor in schizophrenia. A major goal of this work is to assess the extent to which schizophrenia might be preventable by nutritional interventions during gestation.

In this article, we provide brief overviews of the evidence supporting associations between macro- and micronutrient deficiency in schizophrenia. We focus on 3 micronutrients in which there is biological plausibility for a role in this disorder and at least 1 study of an association with schizophrenia. These nutrients include vitamin D, folic acid, and iron. We then discuss the potential implications of these findings for the prevention of schizophrenia. Where possible, we shall report the population attributable risk (PAR) (see Brown and McGrath[4] for a detailed discussion about the limitations of this metric). Drawing on lessons learned from nutritional interventions in other disorders, and the extant biological literature, we shall speculate on relevant factors that bear on the nature, risks, impact, and logistics of various nutritional strategies that may be employed to prevent this disorder.

Studies of Prenatal Exposure to Famine And General Indicators of Malnutrition

In general, if prenatal malnutrition was associated with an increased risk of schizophrenia, then one would predict that the incidence of schizophrenia should be higher

in countries with endemic malnutrition. However, there is a lack of high-quality incidence data from low-income countries.[5] Furthermore, a wide range of epidemiological factors complicate the interpretation of simple ecological analyses of this research question (eg, differential infant and childhood mortality, the influence of comorbid neurodevelopmental disorders, between-site differences in putative protective factors related to rural settings, and cohesive cultural influences). However, in recent years more precise epidemiological studies have been able to explore the association between prenatal exposure to famine and risk of schizophrenia.

The first direct evidence that prenatal ND is related to schizophrenia derived from studies of the Dutch Hunger Winter of 1944–1945, in which a Nazi blockade of the Western Netherlands resulted in an acute period of starvation for most of the inhabitants of that region.[6] Mortality increased 2-fold, and fertility was halved. This was a severe tragedy, though from it came a series of studies on the role of prenatal starvation in health outcomes, including psychiatric disorders. Three key elements made this research possible: precise documentation of caloric food rations, a well-demarcated period of severe famine, and a comprehensive nationwide psychiatric registry. Equipped with these design features, Susser et al[7,8] demonstrated that exposure to severe famine was associated with a 2-fold increase in risk of schizophrenia, coinciding with a peak in risk of Central Nervous System anomalies, including neural tube defects (NTDs). Over a decade later, St Clair and colleagues replicated this finding in 2 regions of China, which experienced a famine during 1959–1961, a result of Mao Zedong's Great Leap Forward.[9,10] Although the Chinese studies did not have precise data on the timing of the exposures, the sample sizes were 10–15 times those in the Dutch study, and the effect sizes found in both Chinese studies were similar to the original Dutch results. Overall, the 3 studies provide strong evidence that prenatal ND plays a role in schizophrenia.

Clearly, severe famine is associated with catastrophic health outcomes for pregnant women and their offspring. The 3 famine studies suggest that offspring who survive severe prenatal restrictions in proteins, calories, and micronutrients have altered brain development that increases their risk of later schizophrenia.

Prenatal Micronutrients And Schizophrenia

Compared with ecological studies related to macronutrition, investigations that document levels of specific micronutrients are likely to offer more promise with respect to the development of preventive strategies for schizophrenia because of the solid body of public health research related to prenatal nutrition and infant outcomes. Although this work is only in its infancy, there are already several intriguing suggestions that prenatal deficiencies of micronutrients are implicated in schizo-

phrenia among offspring. Below, we briefly review these findings.

Vitamin D

The vitamin D_3 system is unique in the sense that its production depends primarily on the action of sunlight on the skin.[11] Ultraviolet B radiation acts on a cholesterol metabolite in the epidermis to produce previtamin D. Subsequent hydroxylations in the liver and kidney create the active moiety (which is a seco-steroid hormone). Vitamin D production is associated with the duration of the photoperiod, which in turn is influenced by latitude and season.[11,12] A minor source of vitamin D is via the diet because certain foods contain vitamin D (eg, fatty fish). Vitamin D can also be obtained via supplements or the consumption of fortified foods (eg, some dairy products). From a global perspective, hypovitaminosis D is one of the most prevalent micronutrient deficiencies.[13]

In order to explore the biological plausibility of low prenatal vitamin D as a risk factor for schizophrenia, an animal model has been developed in which female rats are depleted of vitamin D prior to mating and throughout pregnancy but return to normal diet after the litter is born. This model is called the Developmental Vitamin D (DVD) deficiency model. Neurobiological findings from these animals include larger lateral ventricles, increased cellular proliferation, reduced apoptosis, altered neurogenesis,[14–16] persistent ventricular enlargement,[17] hyperlocomotion in novel environments,[18,19] enhanced locomotion in response to psychomimetic agents, such as the N-methyl-D-aspartate antagonist MK-801[19,20] and amphetamine,[21] increased sensitivity to haloperidol,[19] and altered attentional processing (impaired latent inhibition,[22] altered learning,[23] and altered synaptic plasticity[24]).

Epidemiological Evidence of Vitamin D Deficiency And Schizophrenia

There is growing recognition that vitamin D deficiency is prevalent in many nations.[25,26] Pregnant women are also vulnerable to hypovitaminosis D, due to alterations in outdoor behavior and increased needs of the developing fetus.[27] Ecological studies support a potential role for vitamin D in schizophrenia.[28] These data include studies that have explored the association between schizophrenia and winter/spring birth[29] and also the apparent increased incidence and prevalence of schizophrenia at higher latitudes.[30–32] An additional supportive finding is the observation that dark-skinned migrant groups, who have a higher prevalence of hypovitaminosis D, have an increased risk of psychosis.[5,33,34] Vitamin D deficiency may account for a proportion of the increased risk associated with migrant status.[35]

While the clues from ecological studies make vitamin D an attractive candidate, to date the evidence from

analytical epidemiology is modest. In the first attempt to test this hypothesis, a small pilot study based on 26 cases and 51 controls examined the storage form of vitamin D (25-hydroxyvitamin D) in third trimester maternal sera[36]; however, the results of this pilot study were inconclusive. Based on the Northern Finnish birth cohort study, a link between the absence of vitamin D supplementation during the first year of life and a significantly increased risk of schizophrenia in men was found.[37] Recently, a study based on Danish case-control study examined vitamin D status in neonatal dried blood spots.[38] As expected, the study confirmed that 25-hydroxyvitamin D concentrations showed significant seasonal variation and were significantly lower in the offspring of migrants compared with native-born parents. Overall, the risk of schizophrenia was significantly associated with the level of vitamin D, with lower levels of vitamin D associated with an increased risk of schizophrenia compared with the reference category (fourth quintile). However, the relationship was nonlinear, with the highest quintile of vitamin D also associated with a slightly increased risk of schizophrenia. The PAR for vitamin D in this study was 43.6%. The findings require replication, and the mechanisms underlying the nonlinear association remain to be clarified.

Folic Acid And Homocysteine

As discussed above, a sharp increase in prevalence of both schizophrenia and NTDs was related to periconceptional and early gestational exposure to the Dutch Hunger Winter.[39] A wealth of data suggest that folic acid supplementation, either through vitamins or fortified grains,[40] leads to a marked decline in incidence of NTDs, suggesting that a deficit of this nutrient might be responsible for both schizophrenia and NTDs.

The relationship between maternal levels of homocysteine, an amino acid central to the folate metabolic cycle, and risk of schizophrenia in offspring has been investigated. Although folate levels degrade in stored sera, homocysteine represents an excellent proxy given that levels of this amino acid reliably increase when folate levels decline. Moreover, homocysteine acts as a partial antagonist on the *N*-methyl-ᴅ-aspartate receptor (NMDAR) at physiologic glycine concentrations,[41] consistent with evidence for NMDAR hypofunction in schizophrenia, and hyperhomocysteinemia disrupts placental function, through vasculopathic and apoptotic effects,[42,43] which may compromise oxygen delivery to the fetus. Homocysteine also alters levels of the methyl donor S-adenosylmethionine (SAMe), which regulates the expression of many genes involved in neurodevelopment.[44]

Hence, the relationship between maternal homocysteine and offspring risk of schizophrenia was investigated in the Child Health and Development Study (CHDS) birth cohort in northern California, which had available archived sera drawn during pregnancy in nearly all members of this cohort. Elevated third trimester maternal homocysteine levels were associated with a greater than 2-fold increase in the risk of schizophrenia.[45]

Iron

Iron deficiency anemia (IDA) is one of the most common nutrient deficiencies in pregnant women.[46] IDA is defined as anemia accompanied by depleted stores of iron and signs of compromised iron supply to the tissues. The main etiologies are inadequate dietary intake, an increased requirement for iron, parasitic infections, and loss of blood from other causes.[47] With respect to the global burden of disease, those with tropical diseases are at increased risk of iron deficiency.[48] The global prevalence of IDA during pregnancy is 42%.[49] Pregnancy is known to increase the demands for iron due to expansion of the maternal and fetal blood supply and growth and development of the fetus.

Iron is essential for a plethora of metabolic processes that are essential for optimal brain function. These include its role as a coenzyme of dopamine synthesis and its relationship to dopamine receptor density[50]; dopaminergic abnormalities are a hallmark feature of schizophrenia.[51–53] Iron is also an essential cofactor for synthesis of lipids and cholesterol; this explains disruptions of myelination following prenatal iron deficiency,[54] and these deficits did not improve despite restoration of iron at weaning.[55,56] Intriguingly, myelin and oligodendrocyte abnormalities have been demonstrated in patients with schizophrenia.[57–59] Perinatal iron deficiency also alters the timing and expression of genes that are necessary for development of the hippocampus.[60] Animal experiments have confirmed that pre- and perinatal iron deficiencies are associated with a range of neurobiological outcomes of interest to schizophrenia (eg, working memory, hippocampal size, gene expression, and synaptic plasticity).[61–63] IDA is a risk factor for adverse pregnancy outcomes, including fetal hypoxia, intrauterine growth retardation, and prematurity.[64–68] Moreover, iron deficiency during pregnancy, as well as in infancy and childhood, has long been associated with motor, cognitive, and behavioral abnormalities[69–71] similar to those observed in children who later developed schizophrenia.[72–74]

These suggestions led to the first study specifically aimed at evaluating the role of maternal iron deficiency in schizophrenia. In the CHDS cohort, a mean maternal hemoglobin concentration of 10 g/dl, indicative of maternal anemia, was associated with a nearly 4-fold increased rate of developing schizophrenia, adjusting for maternal education and ethnicity.[75] A dose-response relationship was observed, with a graded increase in risk of schizophrenia correlating with increasing hemoglobin levels.

This association has been recently replicated in a large Danish population–based cohort.[76]

Primary Preventive Approaches

While there remains a paucity of data supporting a role for vitamin D, folic acid, and iron in the etiology of schizophrenia, it is worth noting that the findings reported above on these micronutrients are all based on prospectively acquired data from maternal or neonatal biomarkers and comprehensive follow-up of the offspring for schizophrenia. Nonetheless, of these 3 micronutrients, an attempt to replicate a previous association has been conducted only for iron. Hence, the following discussion on primary prevention of schizophrenia through micronutrient supplementation should be viewed with appropriate caution.

Documenting an association between a prenatal nutrient of potential causal relevance to a disorder in the offspring, though of high importance, is only the first step toward the development of preventive approaches. In our view, implementing a prophylactic nutritional intervention for schizophrenia should be predicated on 4 additional factors. First, what are the types of nutritional interventions that can be implemented, and what is the evidence that such interventions are effective in preventing adverse outcomes during infancy and childhood? Second, what is the "optimum" quantity of intake of such nutrients in pregnancy, when in pregnancy should they be taken, and are there any risks of such supplementation? Third, if the associations between micronutrient deficiency and schizophrenia are confirmed, what is the potential impact of correcting the nutritional intervention on reducing risk of schizophrenia? Fourth, what are the logistics and practicality of such interventions and relative costs for preventing schizophrenia for each of these 3 nutrients? To address these questions, we shall consider lessons learned from nutritional interventions aimed at the primary prevention of other reproductive outcomes.

Vitamin D

With respect to the potential links between vitamin D and schizophrenia, more work needs to be done before any recommendation can be made. Worryingly, there is evidence that the relationship between prenatal vitamin D and neonatal outcomes[77] and schizophrenia[38] is nonlinear. Until the nature of this relationship is resolved, simple public health recommendations are difficult to formulate. In some respects, if the evidence mounts that neonatal and childhood outcomes like bone density can be improved with prenatal vitamin D supplements, this type of evidence is more likely to influence public health bodies to implement more assertive maternal and neonatal supplementation programs. There may

be opportunities for "natural experiments" to explore these issues, much as has been done with interventions related to perinatal folate supplementation and spina bifida or neonatal sleeping position and Sudden Infant Death syndrome.

While the focus of research related to vitamin D and schizophrenia has focused on prenatal exposures, it is feasible that hypovitaminosis D during childhood and adolescence could also impact on mental health.[78] Second-generation dark-skinned migrants to cold climates are exposed to low vitamin D across the life span, thus cumulative prenatal and postnatal exposures may be additive with respect to subsequent risk of psychosis. With respect to first-generation migrants, we lack research that has examined age-at-first-migration and subsequent risk of psychosis. Brain growth is extremely rapid in the first few years of life, thus it is feasible that the absence of vitamin D could disrupt cell cycle kinetics and a range of neurotropic factors.[79] Puberty may also be a window of vulnerability because sex hormones and vitamin D share a broad range of downstream coactivating agents. With respect to prevention, it is possible that supplementation during childhood and adolescence could avert conversion to schizophrenia. While speculative, there is a cogent argument to fast track any type of safe intervention that could possibly result in the primary prevention of schizophrenia. With respect to the potential primary prevention of schizophrenia, vitamin D seems to be an attractive candidate from a public health perspective. It is a cheap, safe, and relatively simple intervention that could potentially avert a wide range of disorders other than schizophrenia.[80,81]

Iron

Several interventions have been employed in previous studies of iron during pregnancy and reproductive outcomes, including iron supplementation via tablets, iron fortification of food, education on health and nutrition, control of parasitic infections, and improved sanitation.[82] Among these, iron supplementation has been most commonly used. These studies have demonstrated that this intervention leads to a substantial reduction of anemia in late pregnancy, at delivery, and 6 weeks postpartum.[83,84]

Iron supplementation appears to lead to favorable perinatal outcomes. Pregnant women with evidence of anemia who were supplemented with daily iron, compared with no/placebo intervention, had an approximately 20% diminished likelihood of having offspring with low birth weight, and birth length was increased by 0.38 cm.[85] However, no differences were found in these outcomes when women were not selected for anemia status and for a number of additional outcomes, including prematurity, placental abruption, preeclampsia, or puerperal infection. Infants whose mothers received

a combination of daily iron and folic acid during pregnancy were 57.7 g heavier than infants from pregnancies without this supplementation[86,87] and were less likely to give birth to offspring of small gestational age.[86]

Data on maternal iron supplementation during pregnancy and neurocognitive and behavioral development in offspring are more mixed. In a systematic review and meta-analysis of 17 randomized controlled trials (RCTs), a modest improvement in IQ in children aged >7 years was observed; however, no effect was observed on the Bayley Mental Development Index and motor development score.[88] In a later study of offspring at age 4, maternal iron supplementation was not associated with improved IQ or behavior,[89] and another study of offspring at age 6–8 indicated no association with mean behavior and temperament scores, although surprisingly peer problems were reported to be greater in the offspring of mothers who received iron during pregnancy than placebo.[90]

While the findings do not show a clear effect of iron supplementation on cognitive and behavioral outcomes, the lack of consistent results may be accounted for by limitations that could be instructive for the evaluation of preventive approaches for schizophrenia. First, all the interventions were applied to general populations rather than targeted for women with IDA. It is possible that if the interventions were targeted to women suffering from anemia, positive effects on child cognitive and behavioral outcomes may have been observed, as was found for birth weight and birth length among mothers who were supplemented with iron in the studies mentioned above.[85] This could be of particular relevance to low-income settings. Hence, although more trials are needed on both anemic and nonanemic populations, these data raise the question of whether efforts should be made to target pregnancies that are vulnerable to iron deficiency. Second, the studies varied by the quantities of iron administered. This raises the question as to the "optimum" quantity of iron to be administered. Current recommendations vary, from 27 mg/day (by the Institute of Medicine) to as much as 60–120 mg/day,[91] depending on how many months of treatment can be achieved during pregnancy, the presence of anemia in the mother, and the prevalence of iron deficiency or anemia in the population. Yet, these recommendations are not based on the dosage of iron necessary to prevent neuropsychiatric outcomes but rather on that needed to prevent anemia in the mother and newborn. The upper limit of iron is based largely on the potential for detrimental side effects, including gastrointestinal consequences such as diarrhea, constipation, and abdominal discomfort,[92] particularly at the higher doses. However, a recent study of iron prophylaxis in pregnancy did not demonstrate any increase in side effects at doses up to 80 mg/day.[93] Third, differences in the period of administration during pregnancy may have accounted for inconsistent results. For schizophre-

nia, associations with iron deficiency were present for both the second and the third trimesters,[75] though clearly more studies will be necessary to confirm that there is a critical "window" of supplementation necessary to prevent this outcome.

Given the lack of epidemiological studies, and the need for more data on the effects of iron supplementation on neuropsychiatric outcomes, we can only speculate on the potential impact of this intervention. Based on the first study of maternal iron and schizophrenia cited,[75] the PAR is 11.6%. These findings suggest that iron supplementation could play an appreciable role in reducing risk of schizophrenia.

Is iron supplementation a practical intervention? A recent randomized controlled trial suggests that approximately 17% of pregnant women given oral iron during pregnancy did not continue iron due mostly to side effects and that 12.5% were noncompliant.[92] In another study of iron supplementation, in rural China, however, compliance was high, with supplements being consumed on greater than 90% of the days on which they were available. Nonetheless, there is a lack of good studies on how well adherence to an iron supplementation regimen would fare in an obstetric practice, and there would clearly be differences depending upon the context, ie, industrialized vs developing country, urban vs rural population, high vs low income, and type of treatment setting.

With regard to cost, iron is remarkably affordable, particularly in comparison with prescribed medications. In a recent study, the cost of 1 iron sulfate tablet (250 mg) was $0.5 (United States), for an average cost for an entire pregnancy of $165.[92] Although there are insufficient data to estimate the potential preventive effect of a prenatal iron supplementation program on schizophrenia risk, this calculation suggests that this intervention is equally to or more affordable than many current diagnostic and therapeutic interventions in obstetric practice.

However, for the billions of individuals who exist on less than $1.25 dollars per day, iron supplementation during pregnancy is unaffordable in the absence of funded public health care programs. Most of the anemia in this group is a consequence of common tropical diseases (eg, hookworm affects over 500 million people). These disorders are amenable to cost-effective coordinated public health packages.[94,95]

Folate

Folic acid supplementation in the prevention of NTDs is one of the major public health success stories of the 20th century. In a recent review by the US Preventive Services Task Force of several large-scale studies, ORs for reductions of NTDs following periconceptional folic acid supplementation ranged from 0.11 to 0.65, indicating a reduction in risk of NTDs between 35% and 89%.[40] These studies included cohort and case-control studies

and RCTs. Periconceptional use of multivitamins containing folic acid have also been demonstrated to decrease the risk of other birth defects, including congenital cardiac anomalies and orofacial clefts.[96,97] These studies included folate prescribed either as part of a multivitamin or as folic acid tablets. Hence, periconceptional folic acid administration has clearly been shown to be of benefit in preventing developmental outcomes, though no known studies have examined folic acid supplementation in relation to neuropsychiatric outcomes other than NTDs.

In 1998, the US Food and Drug Administration introduced a universal prevention program consisting of mandated folic acid fortification (FAF) of enriched cereal-grain products. This represented a sharp departure from the previous policy of targeting pregnant populations with folate supplementation. In an analysis by the Centers for Disease Control and Prevention (CDC) of births from 23 states and Puerto Rico before and after the introduction of FAF, the prevalence of NTDs was reduced by 26%–27%.[98] In Canada, which also instituted FAF in 1998, a 46% reduction of NTDs was reported.[99] Mandated fortification of folic acid in the United States has been related to modest but statistically significant decreases in several other birth defects.[100] Most, but not all, developed nations have mandatory folate supplementation in various food products.[101]

The "optimum" dose of folic acid has yet to be defined. In previous studies of folic acid given as supplements, quantities varied from 0.2 to 0.8 mg/day. In studies of FAF of grains, the recommended US Food and Drug Administration level was 140 µg/100 g,[102] while in Canada fortification was 150 µg/100 g. These amounts were well below those recommended by several established organizations including the CDC, the American Medical Association, and the American College of Obstetricians and Gynecologists, which argued for a substantially greater level of fortification (350 µg/100 g) based on models predicting that the mandated dose would only reduce the rate of NTDs by 20%.[102–104] As noted above, the empirical data exceeded these estimates. However, in a double-blind "dose finding" trial of supplemental folate in the prevention of NTDs, 200 µg/day of folate provided equal effectiveness to 400 µg/day, but 100 µg/day was insufficient.

More recent studies have investigated the role of plasma folate and of folic acid supplements and childhood neurocognition and behavior. Maternal plasma folate was positively associated with children's cognitive test scores in domains that included learning, memory, visuospatial ability, and concentration.[105] In a second study, however, no associations between maternal folate and childhood neurocognitive measures were demonstrated.[106] Folic acid supplementation during pregnancy, obtained prospectively in a population-based birth cohort, was associated with greater verbal, motor, executive

function, and social competence.[107] Maternal dietary folate was associated in another study with improved mental development in children, but the effect was isolated to children of mothers who were homozygous for a mutation in the gene for methylenetetrahydrofolate reductase (*MTHFR*),[108] which plays an important role in folate metabolism.

Until recently, folic acid supplementation was considered to have primarily beneficial effects. Indeed, folate has been shown to maintain genome stability through regulation of DNA biosynthesis, repair, and methylation, and folate deficiency is known to induce and accelerate carcinogenesis by disrupting these processes.[109] This includes its role in remethylating homocysteine to methionine, which is metabolized to SAMe, the principal methyl donor, which regulates gene transcription and protein expression by methylating cytosine. Folate is also necessary for the synthesis of both purines and pyrimidine nucleoside thymidine; folate deficiency, by disrupting the balance between DNA precursors, results in abnormal DNA repair and leads to chromosomal damage by misincorporation of uracil in place of thymidine This process is also associated with increased risk of malignant transformation. Folate supplementation has been associated in retrospective, case-control, and prospective studies with diminished risk of colorectal cancer.[110]

However, evidence is emerging that long-term intervention with folic acid may promote growth of initiated cancer cells.[111,112] This may increase the acceleration of carcinogenesis if folic acid is administered following the emergence of precancerous lesions and subclinical cancers, possibly by providing DNA precursors for growth of cancer cells.[113] In contrast to the previous studies that demonstrated a protective effect on cancer, some observational and controlled folate intervention trials suggest increases in risk of breast, lung, and prostate cancers.[114] Hence, while folate may protect against cancer initiation, there is the potential for this vitamin to facilitate progression and growth of preneoplastic lesions and subclinical cancers. It is also possible, though unproven, that increased methylation of DNA cytosine residues could silence promoter activity, thereby inactivating tumor-suppressor genes or other genes that inhibit carcinogenesis.[115]

With regard to periconceptional folate supplementation, there is recent evidence that this vitamin leads to increased methylation of the maternally imprinted insulin-like growth factor 2 (*IGF2*) gene, possibly due to a relative intrauterine silencing of *IGF2*.[116] An increase in folate intake also has the potential to delay the diagnosis of vitamin B12 deficiency, by correcting the macrocytosis,[117] and to decrease natural killer cell activity from circulating unmetabolized folic acid,[118] though to date no untoward effects of the latter process have been demonstrated. Recently, evidence has emerged linking prenatal

folate supplementation and an increased risk of childhood asthma in the offspring.[119,120]

It should be kept in mind that in most trials of folate supplementation the vitamin is administered to women planning a pregnancy, in order to ensure that periconceptional levels of folate are adequate, but in some studies folate is continued only until the third month of pregnancy. Yet, as noted previously, in the only study to examine the relationship between a biomarker related to folate status—elevated homocysteine—the association was observed only for the third trimester.[121] Universal fortification of folic acid may be helping to address this issue.

With regard to the potential impact of folic acid interventions during pregnancy, we calculated the PAR for elevated homocysteine and schizophrenia. These findings suggest that if folic acid interventions reduced all homocysteine levels to the lowest 2 tertiles of the distribution, the risk of schizophrenia would decline by 29.6% (PAR). Hence, if the association between elevated maternal homocysteine and schizophrenia risk can be replicated, and found to be of similar magnitude, this suggests that folic acid supplementation and/or fortification strategies may have a considerable impact on reduction of schizophrenia risk in the population.

Unlike iron supplementation, the use of universal FAF does not present the same logistical issues with regard to administration of, and compliance with, this nutrient during pregnancy. However, it is unclear whether the FAF initiative implemented over 10 years ago will provide an adequate amount of folic acid to attain an appreciable decrease in schizophrenia risk over the coming decades. In light of this, 1 reasonable option, at least until clearly harmful effects of universal FAF can be demonstrated, would be to continue the current recommendations for folic acid supplementation during pregnancy, even though these women are already receiving universal FAF through the diet. Consideration might also be given to targeted interventions in pregnancies of women with lifestyle, demographic, environmental, and genetic factors that predispose to low folate intake or low blood folate concentrations. These include, eg, smoking, substance use or abuse, obesity, malabsorption diseases, use of antiseizure medications, folic acid antagonists, MTHFR genotype (a known polymorphism of which results in diminished folate levels), personal or family history of NTD, and maternal ethnicity (northern Chinese, native American, and Sikh).[117]

The annual cost of folic acid supplementation or fortification is as low as $12 per pregnancy, over 10 times less than that of iron. Previous cost-benefit analyses of folic acid revealed a net savings of $92 000 for low-level fortification per NTD prevented and $132 000 for folate supplementation per NTD prevented. If lowering homocysteine levels has an appreciable effect of reducing risk of schizophrenia, the cost:benefit ratio for folic acid

interventions may be considerably higher, given that schizophrenia is a far more common outcome.

Conclusion

Evidence from ecological studies has accumulated demonstrating an association with prenatal ND and increased risk of schizophrenia. Other unknown factors must, however, operate alongside micronutrient deficiency; otherwise, we would expect to increased rates of schizophrenia in developing countries compared with advanced economies. While there is a lack of quality epidemiological data on these issues,[5] this does not seem to be the case. It is our view that before preventative approaches can be considered, well-conducted observational epidemiological studies and robust biological evidence supporting the plausibility of specific nutritional risk factors are essential. Nevertheless, although the data are sparse, and while we lack data from randomized controlled trials, initial birth cohort studies with prospectively acquired data suggest that deficiencies of 3 micronutrients that are biologically relevant to pathogenic processes in schizophrenia are associated with an elevated risk of this disorder.

In keeping with findings from nutritional epidemiology in general, some of the findings suggest a nonlinear relationship between the candidate nutritional agent and risk of schizophrenia. As has been found with birth weight and infant mortality, both very high and very low levels can be associated with risk. The gold standard evidence will require randomized controlled trials of prenatal nutritional supplementation and prospective evaluation of mental health outcomes in the offspring. Because the incidence of schizophrenia is relatively low and because the peak age of onset is in the second and third decade of life, these trials will be a challenge. In the decades to come, the research community should be able to explore the associations between prenatal nutrition and offspring mental health using large prospectively collected cohort of mothers and babies (eg, the Norwegian Mother and Child Cohort,[122] the US National Children's Study[123]). Caution is needed when pooling data from different nations because populations from these sites may vary on a wide range of factors (eg, patterns of general nutrition, socioeconomic status, and ethnicity). Thus, the findings from 1 study may not generalize to all populations.

The falling costs of genotyping will also facilitate studies that explore the genetic architecture underpinning candidate micronutritional pathways (eg, polymorphisms that are associated with differential sensitivity to iron, folate, or vitamin D concentrations).[124–126] These clues can contribute to future gene by environment studies, where prenatal nutrition can be included in models that examine maternal and/or offspring genotype.[127]

While one may argue that it is premature to think about preventative nutrient strategies given the relative

paucity of data, in our opinion, such consideration is necessary for 3 reasons. First, an awareness of the merits of nutritional supplementation and food fortification campaigns in the prevention of other disorders may inspire the research community to recognize the importance of conducting prospective studies of prenatal nutrients in schizophrenia in existing cohorts. For example, there is good evidence that prenatal vitamin D supplements can improve a range of bone-related neonatal outcomes.[81] If randomized controlled trials of various prenatal nutritional interventions are commenced, we recommend that neonatal cognitive outcomes be included. Ideally, if feasible, these cohorts could be followed up for later mental illness outcomes. Folic acid supplementation and fortification has played a critical role in reducing risk of NTDs (and possibly other childhood neurodevelopmental outcomes), and iron supplementation has diminished the risk of certain reproductive outcomes. Second, viewing ND and schizophrenia through the lens of a preventative approach may provide researchers with a new tool to evaluate the utility of investigating certain types of micronutrient or other NDs. Considerations in this regard include the prevalence of the exposure in the population (which is probably the most significant determinant of the PAR and number needed to prevent), whether subpopulations exist that may especially benefit from the intervention, whether the intervention can be practically applied in a public health program or obstetric practice, possible adverse effects of the exposure, and affordability as a public health intervention. Finally, if the associations between ND and schizophrenia are confirmed, considering ND from the standpoint of preventative approaches may have utility in the development of public health policies that can be implemented in the near future in order to reduce the incidence of schizophrenia decades from now.

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